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Nonmyeloablative Stem Cell Transplantation for Myelodysplastic Syndrome or Acute Myeloid Leukemia in Patients 60 Years or Older

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ABSTRACT

We analyzed the outcomes of 24 consecutive patients aged ≥60 years with poor-prognosis myelodysplastic syndrome or acute myeloid leukemia undergoing transplantation with nonmyeloablative conditioning using fludarabine (125 mg/m^2) and low-dose total body irradiation (2 Gy) followed by allogeneic peripheral blood stem cell grafts from HLA-identical sibling donors. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and mycophenolate mofetil. The median age of the patients was 64 years (range, 60-71 years). In addition to age, 88% of patients had 1 or more adverse biological features of the disease. With a median follow-up of 21 months, 12 patients are alive, 11 of whom are disease free. The probabilities of 2-year overall and progression-free survival were 52% and 44%, respectively. The cumulative probabilities of relapse and of acute and chronic GVHD were 27%, 45%, and 74%, respectively. Nonrelapse mortality at 100 days and 2 years was 8% and 25%, respectively. Of the 15 patients with extensive chronic GVHD, 1 patient relapsed. These data suggest that nonmyeloablative stem cell transplantation is a feasible treatment option in patients aged ≥60 years with poor-prognosis myelodysplastic syndrome or acute myeloid leukemia. The reasonable disease control with nonmyeloablative transplantation in this high-risk group of patients merits further investigation.

KEY WORDS

Stem cell transplantation • Nonmyeloablative • Older • AML • MDS

INTRODUCTION

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are clonal disorders of hematopoietic stem cells with a median age of onset in the sixth decade of life. The prognosis of AML in older patients is poor, and a cure is rarely achieved with conventional treatment approaches. Although AML is a topic of active clinical investigation, there have been no significant improvements in the survival of older patients with AML [1-8]. Allogeneic stem cell transplantation (SCT) is the only curative option for MDS [9] and has been shown to be of benefit in some groups of younger patients with AML [10]. For the last few years, nonmyeloablative (NMA) or reduced-intensity transplantation protocols have increasingly been used to treat malignant and nonmalignant hematologic disorders [11-15]. These transplantations rely predominantly on a graft-versus-tumor effect rather than myeloablation [16,17]. The major advantage of these protocols is the possibility of extending the procedure to older patients and to those with comorbidities that otherwise would have precluded their candidacy for allografting.

Despite several studies to elucidate the role of NMA or reduced-intensity transplantation in AML and MDS [17-27], only limited data are available in patients aged ≥60 years [28,29]. Older patients with

AML, when compared with younger patients with the same disease, have a poor prognosis and represent a discrete population in terms of disease biology, treatment-related complications, and overall outcome [8]. Therefore, the results of studies that do not address age specifically may not be applicable to older patients.

In this study, we analyzed the outcomes of 24 consecutive patients aged ≥60 years with MDS or AML undergoing NMA SCT with fludarabine and low-dose total body irradiation using HLA-identical sibling donors. The main outcomes of interest were engraftment, regimen-related toxicity, infectious complications, graft-versus-host disease (GVHD), and survival.

PATIENTS AND METHODS

Patients

Between July 2000 and December 2004, 24 patients underwent NMA SCT for MDS or AML at the Princess Margaret Hospital (University Health Network, Toronto, Ontario, Canada). The study was approved by the University Health Network Research and Ethics Board. Each patient and donor signed an informed consent. Eligibility criteria were a diagnosis of AML or MDS, age ≥60 years, availability of an HLA-identical sibling donor, and the patient's willingness to undergo the transplantation. Patients were excluded if they had a history of invasive fungal infection or contraindication to elements of the conditioning regimen. All MDS patients were transfusion dependent and fulfilled the definition of intermediate or high risk according to International Prognostic Scoring System criteria [30]. In addition to age, 88% of the patients had 1 or more poor-prognostic biological features of the disease (Table 1).

Patients with AML were treated with induction therapy and 1 or 2 cycles of consolidation according to previously described institution protocols [5]. Two AML patients referred for transplantation from outside institutions had received a similar type of induction therapy with idarubicin instead of daunorubicin. None of the MDS patients received chemotherapy for disease control before bone marrow transplantation (BMT). Patient-, disease-, and transplant-related characteristics are shown in Table 1. The median age of patients at the time of BMT was 64 years (range, 60-71 years).

Donors

All patients received grafts from HLA-identical sibling donors. Class I (A and B) and II (DRB1) HLA typing on patients and donors was performed by low-resolution molecular testing. The median age of donors was 60 years (range, 45-73 years). The source of stem cells was granulocyte colony-stimulating factor (G-CSF; Neupogen; Amgen, Mississauga, Ontario, Canada)–mobilized peripheral blood mononuclear cells in all patients except one. This donor developed severe side effects on G-CSF and subsequently underwent a bone marrow harvest under general anesthesia. The donors were given 10 μg/kg G-CSF (the dose was rounded to nearest vial size of 300 or 480 μg) subcutaneously for 4 to 5 days, with collection on days 5 and 6. Only 1 collection was required in 85% of the donors. The median numbers of CD34-positive cells infused amounted to 6×10^6/kg recipient body weight (range, 2.5-14.8 $\times 10^6$/kg). There were 5 minor and 2 major ABO mismatches between donor-recipient pairs.

Conditioning Regimen and GVHD Prophylaxis

The conditioning regimen comprised intravenous (IV) fludarabine 25 mg/m^2/d for 5 days (days −5 to −1) and single-dose total body irradiation (2 Gy) on day 0. Unmanipulated peripheral blood mononuclear cells were infused on day 0. GVHD prophylaxis consisted of cyclosporine (CSA) and mycophenolate mofetil (Cellcept, Roche, Mississauga, Ontario, Canada). CSA was started IV at 5 mg/kg/d from day −1. The dose was titrated to maintain trough levels between 200 and 400 ng/mL. The route of administration of CSA was changed to oral as soon as tolerated. CSA taper was started on day 42 in the absence of GVHD. Mycophenolate mofetil was given at a dose of 15 mg/kg by mouth or IV twice daily (dose was rounded to the nearest multiple of 250) from day 0 for 30 days and then stopped without taper. G-CSF was not routinely administered to the recipients.

Supportive Care

All patients were nursed in laminar airflow rooms. Antibacterial prophylaxis was given with co-trimoxazole until neutrophil counts were ≥1 $\times 10^9$/L. For those allergic to co-trimoxazole, ciprofloxacin was substituted. *Pneumocystis carinii* prophylaxis consisted of co-trimoxazole for at least 12 months. The time was extended for patients on prolonged immunosuppression. Pentamidine 300 mg every 4 weeks via aerosol inhalation was substituted for those allergic to or unable to take co-trimoxazole. Acyclovir was used twice daily for 28 days for herpes simplex virus prophylaxis either at 80 mg IV or 400 mg by mouth per dose. Antifungal prophylaxis was not routinely used. All patients were supported with irradiated and leukodepleted blood products. Cytomegalovirus (CMV)–negative blood products were used for CMV-seronegative recipients. Monitoring for CMV was performed in at-risk patients (seropositive recipients or donors) by pp65 antigen testing on a weekly basis for the first 100 days and subsequently on clinic visits up to 1 year or

Table 1. *Patient-, Disease-, and BMT-Related Characteristics*

Patient No.	Patient Age at BMT (y)/Sex	Donor Age (y)/Sex	Diagnosis	Cytogenetics	Pre-BMT Therapy	Disease Status at BMT	High-Risk Features	Acute GVHD	Chronic GVHD	Status at Last Follow-Up	Follow-Up (d)
1	65/F	66/M	AML	Suboptimal	D + A × 1 D + mHiDAC × 2	CR1	High WBC count at diagnosis (47 × 10^9/L)	NE	NE	Died (sepsis)	12
2	66/M	62/M	Relapsed AML	46, XY, del (20) (q11.2)	NOVE-HiDAC × 1	CR 2	Relapsed after autograft for AML	Grade II	Extensive	Died in remission (sudden cardiac death)	1213
3	62/M	48/M	AML-MDS	Diploid	D + A × 1 D mHiDAC × 1	CR 1	Preceding MDS	No	No	Died (disease relapse)	205
4	64/F	53/F	tAML (relapsed)	Not done	D + A × 1	CR 2	Therapy-related AML (breast cancer treated with CT)	No	Extensive	Died in remission (relapse of breast cancer)	283
5	63/F	60/M	AML	Suboptimal	D + A × 1 D + mHiDAC × 2	CR1	—	No	No	Died (disease relapse)	1158
6	67/M	73/M	AML-MDS	Diploid	Ida + A × 1	CR 1	Preceding MDS	No	Extensive	Died (GVHD)	122
7	63/M	49/F	AML	45, X-Y	D + A × 1 D + mHiDAC × 2	CR 1	—	Grade III	Extensive	Died (GVHD)	282
8	63/M	45/F	AML-MDS	46, XY, der(17)t(11;17) (q1 3;p13)	D + A × 1	MDS phase, blasts <5%	Preceding MDS, granulocytic sarcoma	No	NE	Died (disease relapse)	66
9	67/M	54/F	AML-MDS	44~46, XY, add(2)(p21), del(5)(q15q33), −7, −12, −13, add(16)(q24), −19, +2~4mar[cp12]/ 46,XY[6]	AMSA+A × 1 AMSA + mHiDAC × 1	CR 1	Preceding MDS, adverse-risk karyotype	Grade II	No	Died (disease relapse)	191
10	67/M	65/F	Relapsed AML	Diploid	D + A × 1	CR 2	Second remission	Grade III	Extensive	Died in remission (Parkinson disease)	499
11	68/M	65/M	AML	Suboptimal	D + A × 1 NOVE-HiDAC × 1 AMSA + mHiDAC × 1	CR 1	CR after 2 courses of induction therapy	No	Extensive	Alive, in remission	748*
12	61/M	57/M	AML	46, XY[7]/, 47, XY, +8[12]	Ida + A × 1 Ida + mHiDAC × 2	CR 1	Poor-risk karyotype	No	Extensive	Alive, remission	465*
13	71/M	68/M	AML	Diploid	AMSA + A × 1 AMSA + mHiDAC × 1	CR 1	Preceding MPD	Grade II	Extensive	Alive, in remission	329*
14	63/F	48/M	AML	46, XX, add(4)(q3?5)[13]	D + A × 2	CR 1	—	NE	NE	Died (VOD)	20

15	60/F	57/M	tAML	Diploid	D+A × 1 NOVE-HiDAC × 1	CR 1	Therapy-related AML (breast cancer treated with CT and RT), CR 1 with 2 courses of induction	No	No	Alive, in remission	122*
16	65/F	63/F	tMDS	Diploid	Untreated	RAEB (10% blasts)	Therapy-related MDS (cyclophosphamide for Wegner granulomatosis)	No	Extensive	Alive, in remission	1383*
17	65/F	45/M	MDS	43~47, X, add(X)(p22), add(1)(p36), del(5)(q13), add(8)(p23), −10, t(12;15)(q10;q10), add(17)(p11), add(17)(q25), −20, +mar1, +mar2[cp10]	Untreated	RAEB (19% blasts)	High-risk IPSS	No	No	Died (disease progression)	128
18	68/M	64/F	MDS	Diploid	Untreated	RAEB (10% blasts)	Intermediate-risk IPSS	Grade II	Extensive	Alive, in remission	1294*
19	66/F	47/F	Relapsed AML	Diploid	ME × 1	15% blasts	Active disease	No	Extensive	Alive, in remission	548*
20	60/F	58/F	tMDS	46, XX, −3, der(5)t(3;5)(q13.2;q15), +8, del(9)(q22q32)[20]	Untreated	RA with multilinear dysplasia	Previous autotransplantation for relapsed HD, adverse karyotype	Grade II	Extensive	Alive, in remission	911*
21	65/M	58/F	MDS	45, XY, −7[20]	Untreated	RAEB (18% blasts)	Adverse karyotype, high-risk IPSS	No	Extensive	Alive, in remission	391*
22	62/F	60/F	tMDS	45, XX, −7[10]/46, XX[2]	Untreated	RA with trilineage dysplasia	Therapy-related MDS (breast cancer treated with CT and RT), adverse karyotype	Grade III	Extensive	Alive, in remission	315*
23	62/M	60/M	MDS	45~47, X, −Y, +8[cp11]/45, XY[3]	Untreated	RA	Intermediate-risk IPSS	No	No	Alive, in remission	245*
24	60/F	61/M	tMDS	44~45, XX, −3, der(5)t(5;15)(q13;q15), der(6)t(3;6)(q13.2;p23)dup(6)(p21.1p23), −15, +mar[cp6]/46, XX[5]	Untreated	RA with trilineage dysplasia	Therapy-related MDS (endometrial cancer treated with CT and RT), adverse karyotype	Grade III	Extensive	Alive (disease relapse)	141*

BMT indicates bone marrow transplantation; M, male; F, female; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; tAML, therapy-related AML; tMDS, therapy-related MDS; D, daunorubicin; A, cytarabine; mHiDAC, modified high-dose cytarabine; Ida, idarubicin; AMSA, amsacrine; NOVE-HiDAC, mitoxantrone, etoposide, and high-dose cytarabine; M, mitoxantrone; E, etoposide; CR, complete remission; RAEB, refractory anemia with excess blasts; RA, refractory anemia; MPD, myeloproliferative disorder; CT, chemotherapy; RT, radiotherapy; IPSS, International Prognostic Scoring System; WBC, white blood cell; GVHD, graft-versus-host disease; NE, not evaluable; HD, Hogkin disease; VOD, veno-occlusive disease.

*Alive.

according to clinical indications. Preemptive therapy with IV ganciclovir, delivered by ambulatory infusion pump, was started at antigen levels >1/100 000 cells and was continued until 2 consecutive negative levels were taken a week apart.

Definitions and Evaluation of Response

Myeloid and platelet engraftment were defined as the first of 3 consecutive days with an absolute neutrophil count $\geq 0.5 \times 10^9$/L and the first of 7 days with unsupported platelet counts of 20×10^9/L. Patients were evaluable for engraftment if they survived at least 21 days after BMT. Donor cell engraftment was assessed by chimerism studies on unsorted peripheral blood on day 60 and as clinically indicated according to the methods previously described [31].

Patients who survived >14 and 100 days after transplantation were evaluable for acute and chronic GVHD, respectively. The diagnosis of GVHD was based on clinical criteria with histopathologic confirmation whenever possible. The severity of acute and chronic GVHD was scored according to previously defined criteria [32,33]. For study evaluation, the highest grade of GVHD was taken. In addition, the seriousness of GVHD was scored retrospectively according to the criteria recently described by Flowers et al. [34]. Regimen-related toxicity was graded according to the Bearman criteria [35]. Progression-free survival was calculated from the date of BMT to relapse or progression of disease, death from any cause, or last follow-up. Overall survival was calculated from the date of BMT to death or last follow-up.

Statistical Analysis

Data were updated as of May 1, 2005. Results were reported as proportions and 95% confidence intervals (CIs). The Kaplan-Meier method was used to estimate survival [36]. The cumulative incidences of relapse and of acute and chronic GVHD were estimated with the Cmprsk package in R software (The R Foundation, Vienna, Austria). The risk of dying from any cause was treated as a competing event [37]. All analyses were performed with SAS 8.01 (SAS Institute, Cary, NC).

RESULTS

Patient-, disease-, and transplant-related characteristics are shown in Table 1. The median time from diagnosis to BMT was 5 months (range, 2-55 months).

Hematopoietic Recovery and Donor Cell Engraftment

Two patients died before hematopoietic recovery. Five patients' neutrophil counts never decreased $<0.5 \times 10^9$/L, and 8 patients' platelet counts never decreased $<20 \times 10^9$/L. For patients with neutrophil counts $<0.5 \times 10^9$/L and platelets $<20 \times 10^9$/L, the median time to neutrophil and platelet recovery was 13 days (range, 7-27 days) and 12 days (range, 10-34 days), respectively. The median length of hospital stay for BMT was 17 days (range, 10-26 days).

Of the 22 evaluable patients, 20 had chimerism evaluations on unsorted peripheral blood cells on day 60. Fourteen patients demonstrated predominantly donor engraftment, defined as ≥90% donor cells. Of the 6 patients with mixed chimerism (<90% donor engraftment), 3 patients received donor leukocyte infusions. One of these patients changed to predominantly donor chimerism, and the other 2 relapsed. Three patients were not given donor leukocyte infusions because of active GVHD (n = 1), hematologic relapse with bulky disease (n = 1), and donor unavailability (n = 1). There seemed to be a relationship with donor chimerism and relapse risk. Four of the 6 patients with <90% donor chimerism relapsed, compared with 1 of 14 patients with ≥90% donor chimerism.

Regimen-Related Toxicity

Regimen-related toxicities in the first 100 days were grade 1 mucositis (n = 2), grade 1 renal impairment (n = 1), and grade 4 veno-occlusive disease (n = 1). No risk factors for veno-occlusive disease could be identified in this patient on detailed evaluation. In addition, 1 patient developed optic neuritis, which responded to steroids.

Infectious Complications

Culture-positive bacterial infections were observed in 9 (37%) patients in the first 100 days of transplantation. One patient died of sepsis related to a coagulase-negative staphylococcal infection. No probable or proven fungal infections were seen. Six (37%) of 16 CMV-positive recipients experienced reactivation of disease, 3 in the first 100 days of transplantation and 3 beyond 100 days of transplantation. None of the patients developed CMV disease. No CMV reactivation was observed in 3 CMV-seronegative recipients whose donors were seropositive. Other infectious complications were varicella zoster (n = 1) and herpes simplex causing keratitis (n = 1) or mucositis (n = 1).

Graft-versus-Host Disease

Of the 22 evaluable patients, 9 developed acute GVHD grade II (n = 5) and grade III (n = 4). One patient (patient 24) had steroid-refractory acute GVHD. Of the 21 patients evaluable for chronic GVHD, 15 patients had extensive GVHD. Among the patients with chronic GVHD, 1 patient relapsed (patient 24). This patient had therapy-related MDS with

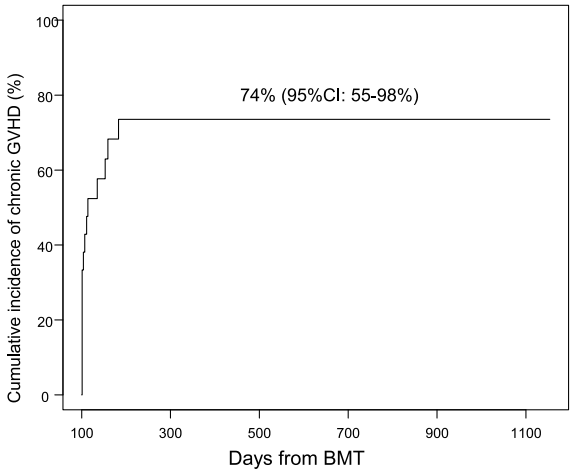

Figure 1. Cumulative incidence of chronic GVHD (the risk of dying from any cause was treated as a competing event).

multiple numeric and structural chromosomal abnormalities. The cumulative incidences of grade II/III acute and chronic GVHD were 45% (95% CI, 28%-73%) and 74% (55%-98%), respectively (Figure 1). None of the patients developed grade IV GVHD. The seriousness of GVHD (acute or chronic) was assessed retrospectively on the basis of a recent study from the Seattle team [34], and 7 patients (44%) were found to have serious GVHD. The serious GVHD in these patients resulted in death (n = 2), prolonged hospitalization (n = 2), and disability affecting activities of daily living (n = 3).

Survival

With a median follow-up of 21 months (range, 4-46 months), 12 patients are alive, of whom 11 are disease free. The 2-year progression-free and overall survival rates were 44% (95% CI, 23%-82%) and 52% (95% CI, 34%-81%), respectively (Figure 2). A plateau in the survival curves has not been observed. Relapses were seen in 6 patients, thus resulting in a cumulative risk of 27% (95% CI, 13%-56%). Twelve patients died. The causes of death were identified as treatment-related mortality (n = 4: sepsis, n = 1; veno-occlusive disease, n = 1; and GVHD, n = 2), relapse (n = 5), and unrelated causes (n = 3: Parkinson disease, n = 1; sudden cardiac death, n = 1; and relapse of primary nonhematologic malignancy, n = 1). Treatment-related mortality at 100 days and 2 years was 8% and 17%, respectively. Overall nonrelapse mortality at 100 days and 2 years was 8% and 25%, respectively.

DISCUSSION

Limited data are available on the outcome of BMT in patients aged ≥60 years with AML or MDS. A recent study from Seattle reported the experience of 52 older patients (≥60 years) with hematologic malignancies who underwent transplantation after myeloablative conditioning [38]. Of the 41 patients with MDS (n = 35) or AML (n = 6) in the study, 14 survived. Although it is difficult to make interstudy comparisons between patients treated with myeloablative versus NMA protocols, the data from our study look encouraging. Our study shows that sustained engraftment is achievable in this group of patients with modest treatment-related mortality and reasonable disease control. Our study cohort included 6 patients with therapy-related MDS (n = 4) or AML (n = 2); 4 of these patients are currently alive and in remission (patients 15, 16, 20, and 22). Of the 11 AML patients who underwent transplantation in first remission, 4 died in remission of transplant-related complications, and 3 relapsed. All 3 AML patients who underwent transplantation in second remission stayed in remission but died of unrelated causes at days 1213 (patient 2), 283 (patient 4), and 499 (patient 10). Two of the 8 patients with MDS relapsed, and there were no treatment-related deaths. As highlighted in Table 1, 88% of our patients had 1 or more poor-prognostic biological risk factors for which long-term disease control is rarely achieved even with intensive conventional chemotherapeutic options. As a result of the limited sample size, we were unable to evaluate the effect of various prognostic factors on outcome.

The cumulative incidence of chronic GVHD was 74% in our study. Only 1 of the patients with extensive chronic GVHD relapsed. However, 5 patients died in remission: 2 deaths were due to direct consequences of GVHD and 3 to unrelated causes. The reasonable disease control with minimal conditioning

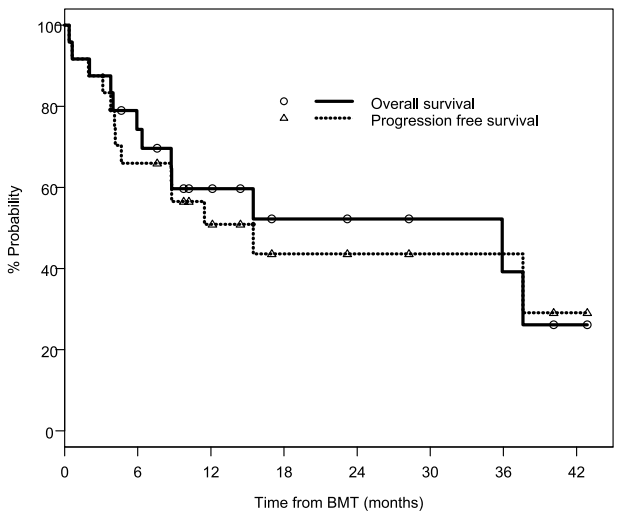

Figure 2. Kaplan-Meier plots of progression-free and overall survival of older patients with MDS or AML undergoing nonmyeloablative stem cell transplantation. The 2-year progression-free and overall survival rates were 44% (95% CI, 23%-82%) and 52% (95% CI, 34%-81%), respectively.

suggests a graft-versus-leukemia effect in these patients.

One of the major limitations of the currently used chronic GVHD classification is an inability to describe the effect of GVHD on overall quality of life. Therefore, we also scored the seriousness of GVHD retrospectively according to recently described criteria by Flowers et al. [34] from Seattle. Of all patients with acute and chronic GVHD in our study, 44% had serious GVHD. A previous study compared the severity, timing, and quality of GVHD among recipients of myeloablative and NMA transplantations. The incidence of chronic GVHD in 2 study cohorts was not significantly different [39]. It is possible that the high incidence of serious GVHD observed in our study is related to advanced age, a concern that should be addressed by future studies with prospective analysis on quality-of-life issues. Selective T-cell depletion and availability of agents such as antithymocyte globulin, alemtuzumab, and anti-CD45 monoclonal antibodies for transplantation protocols may offer the possibility of decreasing GVHD without compromising the graft-versus-leukemia effect [19,40-42].

The pattern of infectious complications (particularly CMV reactivation) in our patient cohort seems to be comparable to those in studies that have evaluated reduced-intensity or myeloablative transplantations in relatively younger patients [43-45]. A major hurdle in the use of BMT from sibling donors is its limited applicability in older patients. It is more difficult to find suitable sibling donors, because the donors are usually old and often have comorbidities that exclude them from stem cell donation [46]. The median age of donors in our study was 60 years. In our experience, the chances of finding a suitable sibling donor for a patient with acute leukemia above the age of 60 years are substantially lower compared with the younger population. Only 10 (14%) sibling donors could be identified from a cohort of 70 patients between the ages of 60 and 70 years treated for AML with intensive therapy at our center. In comparison, the chance of finding an HLA-identical sibling donor for patients younger than 55 years was 42% in a previous study from our center [47]. To increase the applicability, the role of unrelated donors needs to be explored for this patient population. Preliminary observations on a small number of patients suggest that this may be feasible [29,48].

A recent study from the International Bone Marrow Transplant Registry examined the timing of myeloablative SCT from HLA-identical sibling donors in patients with MDS [49]. This study showed that delayed transplantation for low-risk MDS was associated with improved outcome. Conversely, transplantation in early disease is associated with a lower risk of relapse. Although this is speculative at present, a significant reduction in transplant-related mortality by using NMA SCT may allow the possibility of using transplant-related options early in the disease course. Newer agents such as azacytidine and decitabine have been shown to improve marrow function and quality of life and to delay leukemic transformation in patients with MDS [50-52]. Inclusion of these agents in the NMA SCT protocols may further help to improve the efficacy of these protocols in high-risk patients. The overall benefit of these transplantations when compared with conventional chemotherapy options is not clear at present. This question is being addressed in an ongoing prospective international study based on genetic randomization involving multiple institutions in Sweden, Canada, and Germany for patients with AML who are older than 50 years.

In summary, we conclude that donor engraftment is feasible in older patients by using minimal conditioning and can potentially offer reasonable disease control for some patients with poor-prognosis MDS or AML. Although the relapse rate in patients with extensive chronic GVHD was low, the effect of GVHD was debilitating in some patients. These data suggest that NMA conditioning merits further exploration in older patients with MDS or AML. Study designs should considers the concerns related to serious GVHD.

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